(SD2022-151) Engineered Protein Fusions that Bind G4C2 Human Repeats

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OTHER INFORMATION

CATEGORIZED AS

- **Medical**
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ABSTRACT

Researchers from UC San Diego have engineered human zinc finger-containing fusion proteins that target and can destroy or modify human RNA transcripts that contain expanded G4C2 hexanucleotide repeats. This approach, which they have termed zinc fingerdirected RNA targeting, provides a means to, depending on the fusion protein, 1) target and degrade disease-causing RNA transcripts containing G4C2 expansions and to 2) target, label, and track the same transcripts in living cells.

FULL DESCRIPTION

Zinc-finger (ZNF) domain containing proteins (ZNPs) are one of the most diverse and numerous groups of proteins. The zinc-finger motifs within these proteins are maintained by a zinc ion, which coordinates cysteine and histidine in different combinations allowing ZNFs to have the ability to interact with and direct changes in DNA and/or RNA. Recently, a mouse zinc finger protein, Zpf106, has been identified to specifically bind a hexanucleotide repeat expansion, G4C2, in RNA. Naturally occurring G4C2 hexanucleotide repeat expansions within C9ORF72 transcripts have been identified to cause the most common form of familial Amyotrophic Lateral Sclerosis as well as Frontal Temporal Dementia. RNAtargeting

ZNF motifs from the human ortholog of Zpf106, known as ZNF106, can serve as a surrogate RNA-binding motif that can be used to direct human proteins to human RNA transcripts that contain expanded G4C2 hexanucleotide repeats.

Provided herein are fusion proteins, isolated nucleic acids encoding a fusion protein, and gene delivery vectors comprising the same, wherein the isolated nucleic acids comprise: (i) a first sequence encoding a RNA-binding zinc finger domain; and (ii) a second sequence encoding a fusion partner; and methods of using the same.

APPLICATIONS

1) Research tool. To target, locate, and track intracellular or extracellular G4C2 expansion-containing RNA transcripts in fixed or living cells and/or in vivo.

2) Biomarker. Can serve as a pharmacodynamic biomarker to assess efficacy of potential therapies that target G4C2 expansions including small molecules or natural/synthetic compounds and/or any DNA or RNA-targeting gene therapy approach.

3) Therapeutic for disease. To target and destroy disease-causing RNA transcripts harboring G4C2 expansions including those that cause ALS and frontal temporal dementia.

ADVANTAGES

STATE OF DEVELOPMENT

INTELLECTUAL PROPERTY INFO

US 17,777,741 filed 05/18/2022, titled COMPOSITIONS AND METHODS OF USING ENGINEERED FUSION PROTEINS THAT BIND G4C2 HUMAN REPEATS --

https://patents.google.com/patent/WO2021101980A1

UC San Diego is seeking companies interested in commercially applying this patent-pending technology.

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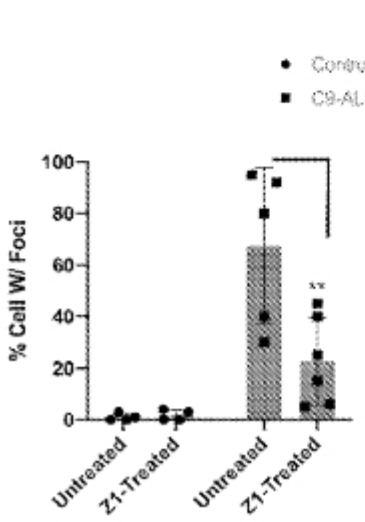
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(54) Title: COMPOSITIONS AND METHODS OF USING ENGINEERED FUSION PROTEINS THAT BIND G4C2 HUMAN REPEATS

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